

Male Reproductive Physiology

THE MALE REPRODUCTIVE AXIS

It is consist of

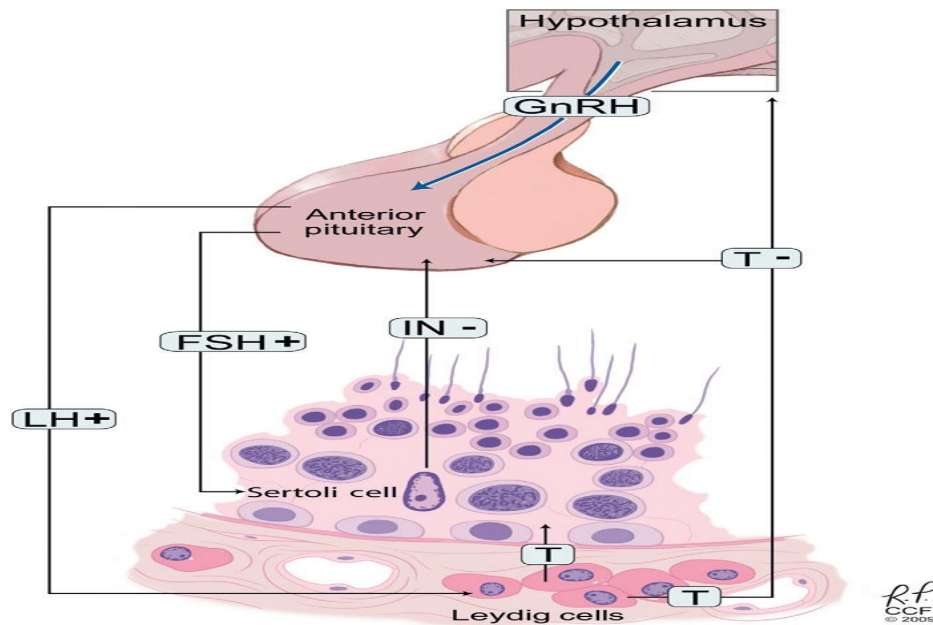
- 1) hypothalamis
 - secretes **GnRH**
- 2) anterior pituitary
 - stimulated by GnRH secretes **LH and FSH**
 - Intrinsic FSH production also occurs
- 3) testis
 - LH stimulates Leydig cells to produce **testosterone**
 - FSH stimulates Sertoli cells to promote **spermatogenesis**

Testosterone in the body

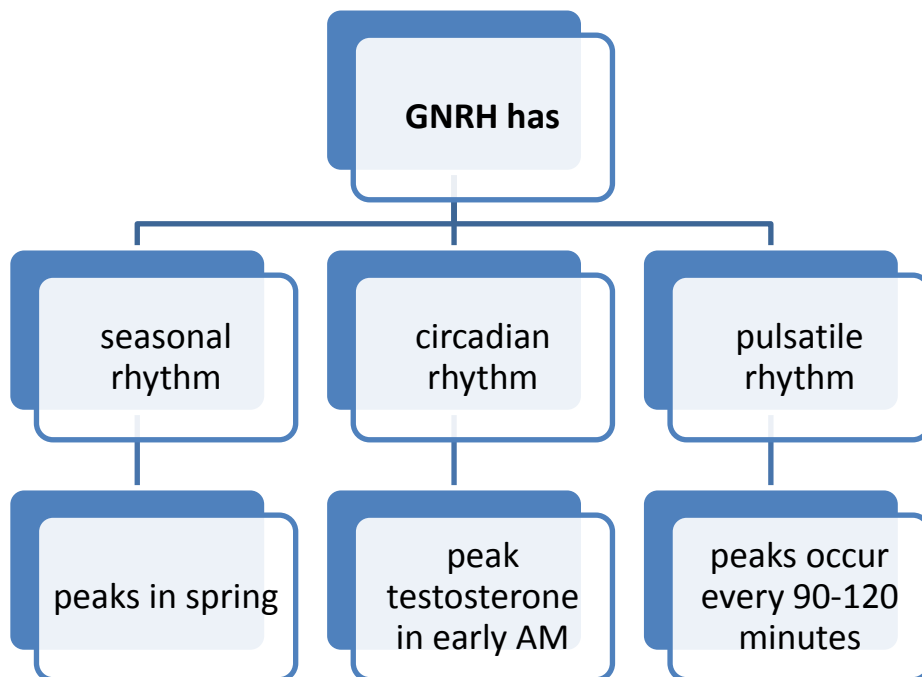
- converted into DHT by 5AR } skin, liver, prostate, etc
- metabolized to estradiol by aromatase } brain, fat, liver, testes

negative feedback

- estradiol acts on *pituitary* to inhibit **FSH** release negative feedback
- testosterone acts on
 - *hypothalamus* to decrease GnRH release
 - the pituitary to decrease **LH**



IN = inhibin B



Hormones regulates Sertoli cell function and spermatogenesis are

- 1) **FSH stimulates Sertoli cells to nurture germ cells through spermatogenesis**
- 2) **testosterone**
- 3) **paracrine signaling from peritubular cells also supports spermatogenesis**

TESTIS

Gross Structures and Vascularization

It measure **15 to 25cc** and ~4.5 to 5.1cm long

It is surrounded by 3 layers surrounding

- 1) tunica vaginalis
- 2) tunica albuginea
- 3) tunica vasculosa

The blood supply

- 1) Testicular (internal spermatic) artery
 - penetrates tunica albuginea then travels inferiorly along the posterior surface of the testicle branches pass anteriorly
 - some branches also travel over inferior pole of testis, passing anteriorly
- 2) Deferential vasal artery
 - from **inferior vesical artery** which is a branch of internal iliac
- 3) cremasteric artery
 - from **inferior epigastric**

*** medial & lateral midsection of testis has fewer vessels than anterior or inferior section ***

Venous drainage

- **Veins DO NOT run with arteries**
- Veins draining parenchyma join deferential veins and form the pampiniform plexus

Innervation

- No somatic innervation
- Autonomic innervation from intermesenteric nerves & renal plexus
 - Runs along testicular artery

*******counter-current exchange of heat in spermatic cord b/w artery & pampiniform plexus provides blood to testis that is 2-4°C lower than rectal temp *******

Cytoarchitecture of the Testis

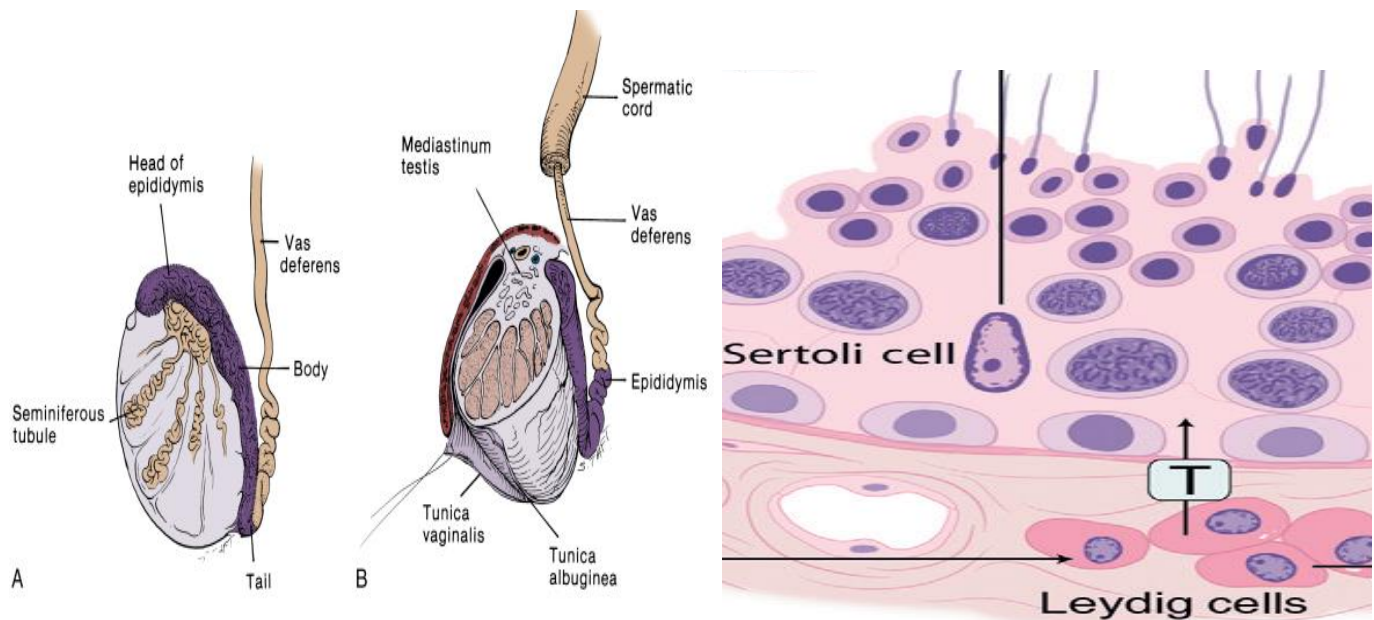
The testicular parenchyma

- septa separates testis into compartments
- each compartment contains **seminiferous tubules 600 to 1200 per testis + interstitial tissue**

1. seminiferous tubules (sertoli cells + germ cells) accounts for ~80% of volume

2. interstitial tissue accounts for 20-30% of the volume of the testicle and consists of:

- Leydig cells (testosterone production by cholesterol transportation into mitochondria)
- mast cells
- macrophages involved in regulation of Leydig cells
- nerves
- blood vessels
- lymphatics
- fibroblastic supporting cell



Seminiferous tubules (peritubular cells)

It is surrounded by

- 1) outer adventitial layer of fibrocytes
- 2) myoid cells interspersed with connective tissue lamellae □ myoid cells have contractile fxn
- 3) thick inner lamella with lots of collagen

It is formed of sertoli and germ cell

A. Sertoli cell

1. Microscopically

- irregular shaped nucleus
- prominent nucleolus
- sits on BM of seminiferous tubules & extends cytoplasmic ramifications towards lumen of tubule
- germ cells are arranged between the Sertoli cells

2. Function :

support germ cell development by

- 1) creates specialized microenvironment of the adluminal compartment of seminiferous epithelium
- 2) supports germ cells via gap junctions between Sertoli and germ cells
- 3) facilitates migration of differentiating germ cells
- 4) **produces androgen-binding protein (ABP)** which serves as reservoir of androgenic hormones

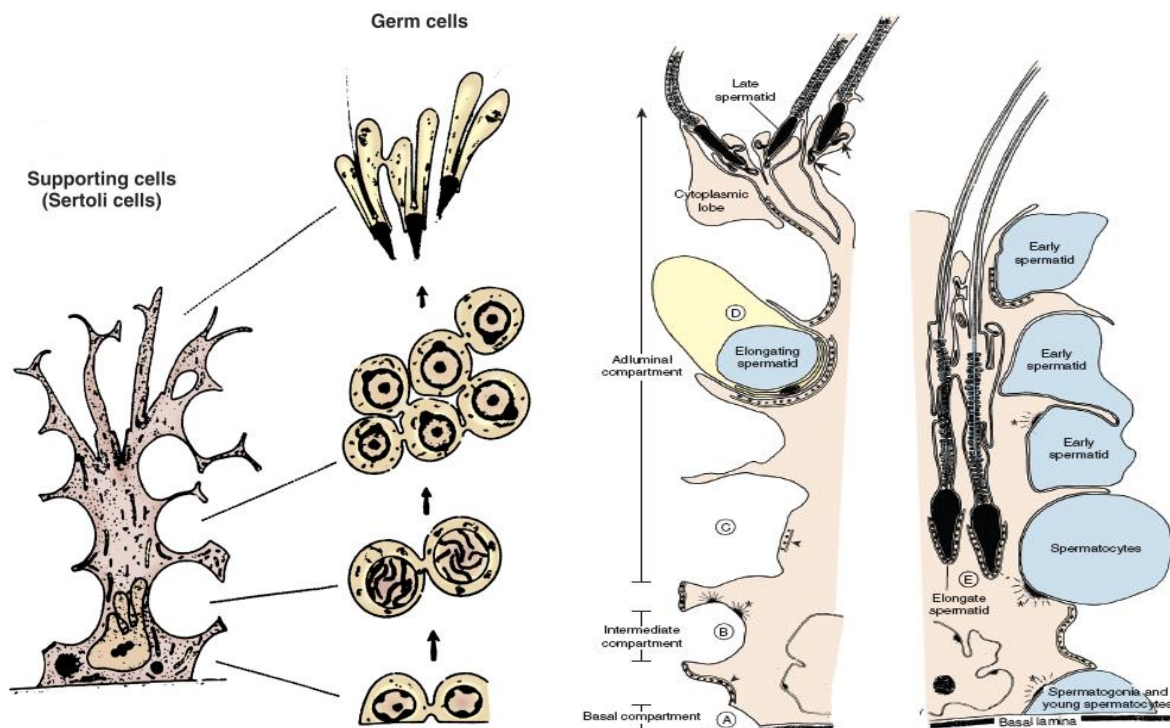
3. Secretion

Inhibin B	activin
32-kD protein hormone	30-kD protein
suppresses FSH secretion	stimulates FSH production
BEST MARKER of the presence of spermatogenesis	

B. Germ cell

Different germ cell types exist in the testis during embryo till puberty

- 1) primitive germ cells called gonocytes □ central location within seminiferous cords
 - 2) gonocytes migrate to periphery and called spermatogonia
 - 3) increased mitotic division at 8th-22nd wk of pregnancy, then again at 7-9 yrs of age
 - 1) dark type A spermatogonia
 - 2) pale type A spermatogonia
 - 3) type B spermatogonia
- ↓ MITOSIS
- 4) primary spermatocytes
- ↓ MEIOSIS I
- 5) secondary spermatocytes
- ↓ MEIOSIS II
- 6) spermatids



tight jxns between Sertoli cells “primary level of barrier” segregates pre-meiotic germ cells (spermatogonia) & young spermatocytes from other germ cells (mature spermatocytes & spermatids)

The blood-testis barrier

its develops at onset of spermatogenesis but germ cells NOT necessary for development of barrier

1. it is formed by

- 1) tight jxns between Sertoli cells “primary level of barrier”
- 2) capillary endothelial cells
- 3) peritubular myoid cells

2. its function are

- 1) keeps stable fluid bathing germinal cells separate from fluid outside barrier
- 2) isolates haploid male gamete which is not recognized as “self” by immune system

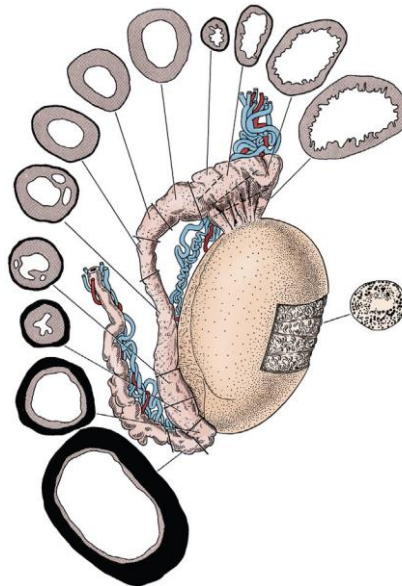
a testicular insult cause anti-sperm antibodies by

- antigens on germ cells are present only after initiation of puberty
- biopsy, torsion, trauma causes antisperm Ab production **ONLY if insult occurs after puberty**

EPIDIDYMIS

Gross Structure and Contractile Tissue

- it is 3-4m in length coiled and convoluted tubule encapsulated within sheath of of the tunica vaginalis
- it is 3 regions:
 - head/caput
 - 8-12 ductuli efferentes and proximal segment of ducuts epididymis
 - body/corpus
 - larger diameter tubule
 - tail / Cauda
 - largest diameter tubule but with irregular shaped lumen
- epididymis is covered by contractile tissue من الرسمة
 - ductuli efferentes to proximal body of epididymis 2-4 cell thick contractile layer surrounds
 - distal body to vas is surrounded by thicker contractile cells
 - tail is surrounded by thick smooth muscle cells that form 3 layers



gray contractile tissue

Black smooth muscle

- epididymis are lined with epithelium consisting of 2 types of cells:
 - principle cells (more numerous)
 - basal cells

blood-epididymis barrier

- it is a gap junctions between epithelial cells form a blood-epididymis barrier
- extends head to tail

Vascularization

	head & body	tail	
Arterial supply	branch of testicular a. divides into superior & inferior epididymal branches	branches from vas deferential artery	cremasteric artery serves as collateral
venous drainage	veins join pampiniform plexus or vena marginalis	veins join to form vena marginalis epididymis of Haberer	
Lymphatic drainage	same as testis	join lymphatics of vas deferens to external iliac nodes	

Innervation

- primarily from **intermediate spermatic nerve (br. of superior part of hypogastric plexus)** and **inferior spermatic nerve (branch of pelvic plexus)**
- number of nerve fibers increases as you move distally towards tail

Functions of the Epididymis

1) sperm transport (2-12 days)

- transit time is age independent , it is more depends on sperm production rate (higher = faster)
- transport is primarily due to contractile cells surrounding epididymis NOT sperm
- time through tail is same as the time it takes to get through head and body

2) sperm storage

- viable sperm stored in tail for varying lengths of time up to several weeks, depending on sexual activity
- ~ 50% of epididymal sperm is in tail

3) maturation of spermatozoa

1. motility

- **partly time dependent but mainly due to interactions in distal region**
- head has mostly “immature” tail movement; tail >50% of spermatozoa have mature motility

2. fertilization

- **worst fertilizing capacity in head, best in tail**
- fertility maturation occurs at level of distal body/proximal tail
- testicular spermatozoa can't fertilize unless ICSI used

Biochemical changes do spermatozoa undergo during transit through the epididymis that lead to ↑'d ability to adhere to zona pellucida

- A. sperm surface membranes become more negatively charged
- B. oxidation of membrane sulfahydryl group to disulfide bonds
 - provides rigidity for motility and penetration
- C. increased capacity for glycolysis

factors controls epididymal function

- A. DHT and 5 α -reductase in epididymis
- B. temperature so important considerations for cryptorchidism and varicocele
- C. sympathetic innervation

DUCTUS VAS DEFERENS

- derived from the mesonephric (Wolffian) duct
- 30-35cm in length, 2-3mm in diameter (lumen 300-500µm in diameter)
- starts at epididymal tail & terminates in ejaculatory duct near prostate
- 5 segments:
 - 1) sheathless epididymal portion
 - 2) scrotal portion (convoluted and straight)
 - 3) inguinal division
 - 4) retroperitoneal/pelvic portion
 - 5) ampulla
- 3 layers
 - 1) outer adventitial connective tissue sheet (contains blood vessels & small nerves)
 - 2) middle layer consisting of 3 layers of muscle □ **vas has greatest muscle-lumen ratio (10:1) of any hollow viscus**
 - 3) inner mucosal layer
 - pseudostratified epithelium
 - 1) basal cells
 - 2) principal cells □ more common in proximal vas
 - 3) pencil cells
 - 4) mitochondrion-rich cells □ more common in distal vas

blood supply deferential artery □ **branch of inferior vesicle artery**

innervation

- **sympathetic** rich supply of sympathetic adrenergics from hypogastric nerves
 - cause muscular contractions resulting in propulsion of sperm
- **parasympathetic** minor contribution nerve fibers

function “depends on androgen stimulation T converted to DHT in epididymis”

- spermatozoal transport by muscular contraction
- **stores almost as much spermatozoa as epididymis**
- absorption and secretion

SPERMATOOZOA

The process of spermatogenesis

- it take 64- 72 days □ 4 cycle each (16days)
- 3 main phases:
 - a. proliferative phase
 - spermatogonia** divide either to
 - replace their numbers (stem cell renewal)
 - produce daughter cells committed to become spermatocytes (mitosis)
 - ****2/3 of all spermatogonia undergo apoptosis****
 - b. Meiotic phase
 - spermatocytes** undergo reduction division resulting in haploid spermatids (meiosis)
 - c. Spermiogenesis
 - spermatids** undergo metamorphosis in size & shape to form **mature spermatozoa which include**
 - loss of cytoplasm
 - formation of acrosome
 - formation of flagellum
 - migration of cytoplasmic organelles to positions characteristic of the mature spermatozoon

Spermatozoa is characterized by

- 60µm long
- **head**
 - oval (4.5µm long x 3µm wide)
 - consists primarily of **nucleus & acrosome**
 - **acrosome is 40-70% of the head**
- **connecting piece**
 - links head to middle piece
- **middle piece**
 - consists of highly organized helically arranged **mitochondria** surrounding the outer dense fibers and the characteristic **axoneme “9+2 microtubular structure of sperm”**
- **tail (principal piece)**
 - consists of outer dense fibers and axoneme covered by fibrous sheath
- **end piece**
 - only axonemes



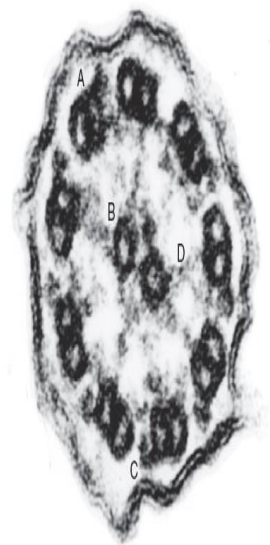
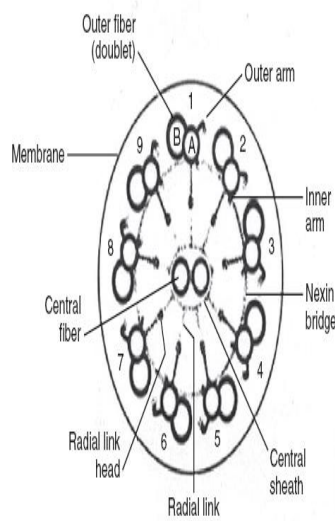
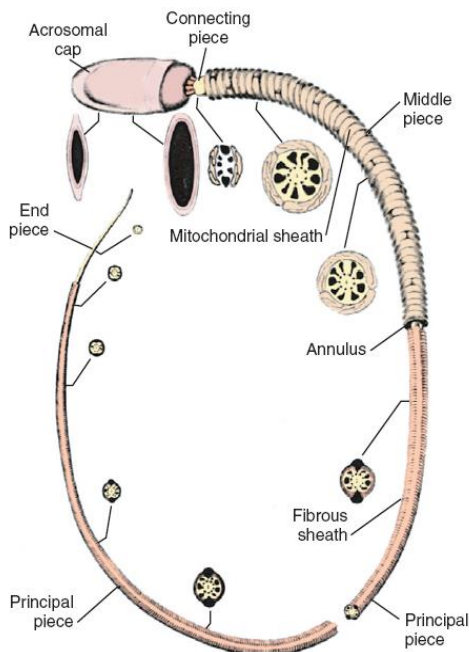
Head
Length: 5–6 µm
Width: 2.5–3.5 µm

Acrosome: 40%–70% of head

Midpiece
Width ≤ 1 µm
Length 1.5 x head length

Tail
Approximately 45 µm long
Uniform
Thinner than midpiece
Uncoiled
Free from kinks

Cytoplasmic droplets
Less than one half of head area
In midpiece only



The “9 + 2” sperm axonemal structure

Sperm motility defects, termed ciliary dyskinesias, are common and can be either

- correctable (nonspecific flagellar anomalies)
- genetic (dysplasia of the fibrous sheath).

Organs contribute to normal ejaculate

- initial fluid
 - glands of Littre (periurethral glands)
 - Cowper's glands (bulbourethral glands)
- 2nd portion of ejaculate
 - prostate
- last portion
 - testes, epididymis (**most of sperm**),
 - vas,
 - **SV (70% of overall ejaculate)**

Source	Volume	Components
Testes	< 1%	Sperm
SV	1.5 – 2 mL	Fructose, PGs, base (EDO = acid semen) coagulation factors
Prostate	0.5 mL	Zn, citrate, PSA, acidic (coagulum lysis)
Cowper's and Littre glands	0.1 – 0.2 mL	Liquefaction factors

- ejaculate is initially able to **coagulate** (seminogelin from SV) then **liquefies** due to proteases (eg PSA) assists in passing through cervical mucous
- uterine transport takes 5-68 minutes
- **capacitation occurs within female genital tract** and results in the **acrosome reaction** and the development of hyperactivated motility

pH of ejaculated semen is slightly alkaline (7.3-7.7)

- SV secretions are alkaline “main component of ejaculate”
- however, prostatic secretions are acidic

the major factors responsible for semen coagulation

- fibrinogen, factor 12, prothrombin (factor 2), etc
- Semenogelin”secreted from SV”

the major proteolytic enzymes in semen

1) PSA

2) plasminogen activators

3) pepsinogen

4) lysozyme

5) α -amylase

6) hyaluronidase

Causes of low fructose levels (<120mg/dL) in semen

- 1) inflammation of SVs
- 2) androgen deficiency
- 3) partial obstruction of ejaculatory ducts
- 4) incomplete ejaculation

Male infertility

Definition

It is the inability of a sexually active, non-contracepting couple to achieve spontaneous pregnancy in one year

Incidence

15% of couples suffer from infertility.

- 20% of infertility due to male factor alone
- 30-40% of infertility involve both M & F factors
- 50% of infertility cases involve female factor
 - **ovulatory dysfunction & fallopian tube abnormality account for majority**

the goal of the evaluation is to identify

- 1) reversible conditions
- 2) irreversible causes that may be managed by ART using male partner's sperm
- 3) irreversible conditions that necessitate donor insemination or adoption
- 4) significant underlying medical pathology
- 5) genetic and/or chromosomal abnormalities that may affect either patient or offspring

Prognostic factors for male infertility are:

- DURATION OF INFERTILITY
- PRIMARY OR SECONDARY INFERTILITY
- RESULTS OF SEMEN ANALYSIS
- AGE AND FERTILITY STATUS OF FEMALE PARTNER

Female age is the most important single variable influencing outcome in assisted reproduction

Causes of male infertility

1) Endocrine causes (Pre-testicular)

- ☐ Hypothalamic } Isolated hypogonadotropic hypogonadism (Kallman's syndrome)
 - } Prader-Willi (low GnRH)
 - } Laurence-Moon-Bardet-Biedl (AR)
- ☐ Pituitary disease } pituitary surgery, infarction, tumours, rads, infectious disease
 - } Fertile eunuch syndrome (isolated LH deficiency)
 - } Isolated FSH deficiency
 - } PRL excess (adenoma)
 - } Cushings (Glucocorticoid excess)
- ☐ Androgen excess } endogenous, exogenous
- ☐ Estrogen excess } obesity, adrenal tumours, Sertoli/Leydig tumours, liver failure
- ☐ Adrenal/Thyroid abnormalities
- ☐ Abnormalities of androgen action } deficiency of androgen synthesis
 - } defect in T ☐ DHT conversion (5AR deficiency)
 - } defects in AR ☐ 46XY male pseudohermaphrodite,

2) Disorders of spermatogenesis (Testicular)

- ☐ Chromosomal disorders } Klinefelter's
 - } XX Male
 - } XYY syndrome (supermale)
 - } Noonan's syndrome, Down's syndrome
 - } Y chromosome microdeletions
- ☐ Genetic } prune belly, myotonic dystrophy, AIS
- ☐ Congenital } UDT, intersex, bilateral anorchia, SCO syndrome
- ☐ Vanishing testis syndrome
- ☐ Testicular torsion
- ☐ Varicocele
- ☐ Orchitis
- ☐ Gonadotoxins } Chemo/radiation, Heat, Environmental toxins, Medications, Idiopathic

3) Disorders of sperm delivery (Post-testicular)

- ☐ Ductal obstruction } ED obstruction ☐ ejaculatory duct cyst, utricle cyst
 - } Vasal obstruction ☐ vasectomy, injury w/ hernia repair, CF, CBAVD, infection (TB, smallpox)
 - } Epididymal obstruction ☐ CF, TB, smallpox, epididymitis, Young's syndrome
- ☐ Ejaculatory disorders } retrograde ejaculation (TURP, TURBN, DM, spina bifida, α -blockers, neurotoxic drugs, MS)
 - } neurologic abnormalities (SCI, spina bifida, post-RPLND)

4) Sperm function disorders

- ☐ immunologic disorders (eg Antisperm Ab's)
- ☐ ultrastructural abnormalities of sperm

i. Endocrine Causes (2nd spermatogenic failure)

It is secondary to hormone deficiency, hormone excess, or receptor abnormalities

A. Hypothalamus causes

1- Isolated hypogonadotropic hypogonadism

1) **idiopathic hypogonadotropic hypogonadism**

- no known cause

2) **Kallmann syndrome (congenital hypogonadotropic hypogonadism + anosmia)**

- hypothalamus can't produce GnRH } X-linked recessive

Clinical picture

hypogonadism +

- anosmia
- renal anomalies
- craniofacial anomalies (cleft palate, congenital deafness, etc)

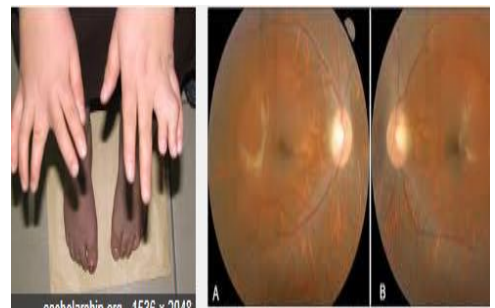
2- **Prader-Willi syndrome (15q11-13)**

- كل حاجه فيه صغيره طولہ ايده رجله عقله عضلاته ضعيفه وتخين + Hypogonadism
- Obesity
- hypotonic musculature
- mental retardation
- small hands and feet
- short stature



3- **Laurence-Moon-Bardet-Biedl syndrome**

- hypogonadotropic hypogonadism +
- retinitis pigmentosa
- polydactyly
- anosmia
- hypomnesia
- short



B. Pituitary causes

1- pituitary disease

- It may be caused by :

- surgery
- infarction
- radiation
- infectious disease
- tumours

- pituitary tumours can present with galactorrhea , infertility, ED, visual field disturbances, and severe H/As
- **small & soft testes** (vs small and firm in primary testicular failure)
- **T usually low or low normal and FSH, LH are low**

2- Fertile Eunuch Syndrome

□ isolated LH deficiency (normal FSH, low testosterone)

- lack of LH → no Leydig cells → no testosterone → lack of virilization , small-volume ejaculates , oligospermia
- large testes افتر

3- isolated FSH deficiency

- N LH and testosterone levels → N virilization and testes
 - no FSH → oligospermia, azoospermia } usually have <5million/mL
- Rx □ recombinant human FSH for spermatogenesis

C. estrogen excess

- ☐ excess estrogens suppress pituitary gonadotropin secretion causing **2° testicular failure**
- estrogen-secreting adrenal or testis tumours,
- hepatic dysfunction
- obesity

Rx aromatase inhibitors (eg ketoconazole)

D. androgen excess

- ☐ androgen excess causes hypogonadal state by -ve feedback, leading to **2° testicular failure**
- 1) exogenous androgens eg anabolic steroids
- 3) endogenous androgen production as in CAH testicular or adrenal tumours

E. prolactin excess

- **causes**

- ☐ **idiopathic**
- ☐ **pituitary tumour**
- ☐ **meds (dopamines, INH, TCA)**
- ☐ **stress**
- ☐ **elevated TSH**
- ☐ **medical illness (renal failure, cirrhosis)**

- low FSH, LH and testosterone

Rx ☐ bromocriptine, cabergoline (recommended)

☐ surgery, rads

F. thyroid disease

- hyperT4 alters spermatogenesis and sex steroid hormone metabolism
- hypoT4 effects are more subtle and reversible

G. glucocorticoid excess

- cortisol excess suppress LH,

H. androgen abnormalities

- may involve;

1) deficiency in androgen synthesis

2) deficiency in conversion of T to DHT (5 α -reductase deficiency)

3) androgen receptor abnormalities } eg AIS

☐ X-linked genetic disorder caused by mutation in androgen receptor gene

☐ 46, XY male w/ phenotypes ranging from pseudohermaphroditism to N male with infertility

☐ **elevated testosterone levels**

ii. Disorders of Spermatogenesis (PRIMARY SPERMATOGENIC FAILURE)

It is a testicular deficiency as a consequence of primary spermatogenic failure is caused by conditions other than hypothalamic-pituitary disease and obstruction of the male genital tract.

Incidence It is the commonest form of reduced male fertility

Causes

A. chromosomal disorders ,

كلهم عندهم elevated FSH , LH , low T azospermia وعلاجهم adoption/donor sperm

1) Klinefelter's Syndrome العادي وممكن يبقي عنده

☐ **low testosterone , N in 50%,**

Rx ☐ microTESE + IVF/ICSI (sperm found 50%)

2) Noonan's syndrome الغادي

3) Y chromosome microdeletions see later

4) XX male العادي

5) XYY syndrome

☐ **tall men** w/ increased incidence of **UDT & hyospadias** } ?aggressive, criminal

☐ **severe oligospermia or azoospermia**

☐ **maturation arrest or Sertoli cell-only on Bx**

☐ **normal FSH, LH , and testosterone**

Rx ☐ ART

B. bilateral anorchia (aka vanishing testis syndrome)

- have prepubertal male phenotypes (androgens and MIS were present in utero)

- testes lost in utero due to infection, torsion, or vascular injury

- elevated FSH, LH and low testosterone

Rx ☐ testosterone for virilization + adoption/donor sperm

C. Sertoli Cell-only syndrome (SCOS)

- seminiferous tubules with no germ cells
- small to normal testes
- **azoospermia**
- **elevated FSH with normal testosterone and LH**
- **can successfully retrieve sperm in 50% of SCOS patients ????**

causes of SCOS

- **idiopathic (most common)**
- Y microdeletions
- karyotypic abnormalities
- UDT
- orchitis
- chemo or Rads
- estrogen Rx

D. testicular torsion

- severity of semen abnormalities related to duration of torsion
- there may be abnormalities even in contralateral normal testes

E. UDT see later

F. varicoceles see later

G. orchitis

- may also be due to mumps syphilis, gonorrhea, leprosy, and mononucleosis
- Rx ☐ IFN treatment during orchitis decreases likelihood of atrophy
- ☐ long-acting GnRH analog
 - ☐ TESE + IVF/ICSI

H. CHEMO

- affects most actively dividing cells □ spermatogonia and spermatocytes
- **alkylating agents have worst effect** on spermatogenesis (eg cisplatin, cyclophosphamide)
- **develop azoospermia and elevated FSH**
- after chemo, **most recover spermatogenesis within 4 yrs** with **no increased risk of birth defects**
- bank sperm before, not during, chemo □ chromosomal aneuploidy seen during chemo

I. RADs

- germ cells are very radiosensitive □ spermatids more resistant than spermatogonia & spermatocytes
- **Leydig cells are relatively radio-resistant → testosterone levels normal**
- **semen quality returns to normal within 2 yrs after RADs for seminoma with no increased risk of birth defects**
- **25% become permanently infertile**

J. febrile systemic illness

- can impair spermatogenesis for ~3months
- recommend avoiding saunas, Jacuzzis, or hot tubs □ type of underwear NOT issue

K. toxins

- lead
- mercury
- arsenic
- cadmium
- pesticides
- hydrocarbons
- amebicide soil fumigants

L. Drugs

Drug	Effect
Cocaine	Oligospermia
Marijuana	↓testosterone, Oligospermia
chronic opioid use	hypogonadotropic hypogonadism
Smoking	decreased semen parameters
Alcohol	decreased # of germ cells, decreased bioavailable T
caffeine	controversy may affect motility
Sulfasalazine	Oligoathenospemia
Nitrofurantoin (chronic high doses)	maturation arrest
Colchicines	Oligospermia
Cimetidine	degeneration of germ cells
CCBs	affects sperms ability to fertilize egg (no effect on production)
Anti-androgens	
finasteride ???	
Spirolactone (anti-androgen activity)	
Steroids	

iii. Sperm Delivery Disorders

It include

- 1- ductal obstruction see obstructive azospermia
- 2- ejaculatory problem
 - suspect ejaculatory problem in patients with **low volume or absent ejaculate**
 - post-ejaculate urine for sperm ☐ **+ve if 10-15 sperm/HPF**
- 1) failure of emission ☐ SCI, MS, retroperitoneal sx
- 2) retrograde ejaculation ☐ BN surgery, TURP, DM, MS

iv. Sperm Function Disorders

A. ultrastructural abnormalities of sperm

- 1) **defects seen on electron microscopy** ☐ defects in outer dense fibers, microtubules, mitochondria, connecting piece, acrosome
 - 2) **defects in flagellum** ☐ immotile but viable sperm
 - ☐ can be associated with defects of cilia of respiratory tract
 - primary ciliary dyskinesia
 - if associated with situs inversus also then called Kartagener's
 - 3) **defects in sperm head** ☐ round-headed sperm (globozoospermia) can't fertilize egg
 - 4) **defects of connecting piece** ☐ separation of head from tail
- Rx ☐ IVF/ICSI

B. immunologic infertility

formation of anti-sperm Ab's is prevented by blood testicular barrier which is developed at puberty

incidence

- 10% of infertile males
- 2% of fertile males

RFs for developing anti-sperm Ab's

- 1) Varicoceles
- 2) Cancer of testis
- 3) Bx or surgery of testis
- 4) UDT
- 5) Torsion
- 6) GU tract infection (mumps, epididymitis)
- 7) Obstruction of the ductal system
 - vasectomy ☐ 60% develop anti-sperm Ab's
 - CBAVD ☐ 1/3 have anti-sperm Ab's
- 8) Trauma to GU organs
- 9) Anal intercourse (receptive)

anti-sperm Ab's affect sperm

- motility
- cervical mucous penetration
- capacitation
- acrosome reaction
- binding to and penetration of the zona pellucida
- oolemma binding

In treatment of immunological infertility

- 1) suppress Ab formation ☐ corticosteroids (don't improve fertility in most)
- 2) use of spermatozoa without Abs for ART ☐ chymotrypsin to digest off Ab's

So the best treatment

- ☐ IUI + chymotrypsin
- ☐ IVF/ICSI

Initial w/u for male infertility

1) History

previous fertility/infertility hx - Duration - Prior conceptions - Current or previous partner - Previous fertility evaluation and treatment	sexual hx - Duration of sexual relations with and without birth control - Methods of birth control - Erectile function - Use of Lubricants - Frequency/timing of intercourse	Medical Past history - Diabetes mellitus - Neurologic disease - Spinal cord injury - Multiple sclerosis - Infection - o Urinary infections - o Sexually transmitted disease - o Epididymitis/prostatitis - o Tuberculosis - o Mumps orchitis - o Recent viral/febrile illness - Renal disease - Chemotherapy/radiotherapy
Surgical past history - o Orchidopexy, torsion - o Retroperitoneal/pelvic surgery - o Herniorrhaphy - o Vasectomy - o Bladder neck/prostatic surgery	Medications - o Gonadotoxins ▪ Environmental exposures (pesticides, heavy metals) ▪ Habits (tobacco, recreational drugs, anabolic steroids)	occupational hx - laptop use, - exposure to chemicals, heat, etc
Developmental history - Childhood - Cryptorchidism - Onset of puberty, gynecomastia - Testicular torsion or traum	FmHx ▪ hypogonadism, ▪ UDT, ▪ CF ▪ congenital midline defects	female reproductive hx ▪ previous pregnancies and off spring w/ other partners, ▪ menstrual hx, ▪ infertility w/u

2) Physical exam

- ☐ general } VS's, body habitus, virilization, gynecomastia (estrogen), visual fields, etc
- ☐ abdo exam } retention, masses
- ☐ neuro exam } motor, sensory, reflexes, peripheral neuropathy
- ☐ CV exam
- ☐ genital exam
 - ☐ phallus } hypospadias, severe chordee
 - ☐ testes } mass, volume/size (normal is 4x3cm or 15-25cc)
 - ☐ epididymis } presence of head, body, tail and induration or cystic dilation
 - ☐ vas deferens } presence, areas of atrophy
 - ☐ spermatic cord } varicocele
 - ☐ hernias
- ☐ DRE
 - ☐ mass, cystic dilation of SV, prostatitis

3) Investigations

- ☐ semen analysis x 2
- ☐ hormonal evaluation (**if sperm is <10 million/cc**)
- ☐ other (**NOT ROUTINELY RECOMMENDED**)
 - urinalysis & urine C&S
 - leukocyte staining
 - semen cultures
 - post-ejaculatory urine (PEU) specimen
 - anti-sperm Ab
 - genetic testing (karyotype, CF mutation, Y microdeletions)
 - Ultrastructural Evaluation
 - sperm functioning tests
 - DNA Fragmentation Index } >30% is bad
 - post-coital test (PCT) } normal is >10-20 sperm per HPF
 - acrosome reaction test } N = LOW spontaneous reaction rates (<5%) + HIGH induced reaction rates (15-40%)
 - sperm penetration assay (SPA) } remove zona pellucida & assess penetration
 - hemizona assay } index <0.6 likely means sperm-zona interaction problem
 - sperm viability assay } to assess whether non-motile sperm are dead or viable
 - reactive oxygen species (ROS) testing } elevated levels can cause sperm damage

4) **imaging**

- ☐ TRUS (for low ejaculate volume)
- ☐ scrotal U/S (if scrotal exam is difficult or testicular mass suspected)
- ☐ pelviabdominal U/S
- Vasography
- Venography

Both partners should be investigated simultaneously.

Basic investigation

1. **Semen Analysis** *** it is recommended that all patients should have at least 2-3 S/A's
*** at an interval of 2-3 months

Precaution in specimen collection

- keep same # of days of abstinence for each collection (2-7)
 - can affect counts, volume BUT DOES NOT affect motility & morphology
- no creams or lubrication
- collect all specimen
- clean wide mouth containers
- can be done at home but keep warm in transit □ should be given to lab ~1hr after collection

Macroscopic Features of Semen Analysis

PARAMETERS	NORMAL VALUES	ABNORMALITIES	CLINICAL SIGNIFICANCE
Ph	7.8	Acidic: <6.5-7	With low volume and noncoagulation: congenital bilateral absence of vas deferens Ejaculatory duct obstruction Partial retrograde ejaculation
Coagulation/liquefaction	Coagulates and liquefies within 20 minutes at room temperature of 37° C	No coagulation Prolonged liquefaction	Congenital absence of the seminal vesicles Poor prostatic secretions
Color	Whitish-gray; pearl-white	Yellowish color Reddish brown	Jaundice, carotenemia, drugs Haemato-spermia secondary to urethral bleeding or inflammation of the seminal vesicles, exclude genitourinary tumors
Viscosity	4-mm threading	>6 mm No threading	Important when associated with low motility
Volume	2-4 mL	0 (aspermia) <2 mL (hypospermia) >4 mL	Retrograde ejaculation Incomplete collection Partial retrograde ejaculation Short duration of sexual abstinence Prolonged sexual abstinence

Table 21–4.**Characteristics of Normal Semen
(World Health Organization, 1999)**

Color	White, opalescent
Specific gravity	1.028
pH	7.35-7.50
Volume	2-6 mL
Count	2×10^6 spermatozoa/mL or more
Motility	$\geq 50\%$ motile (grades A + B) or 25% with progressive motility (grade A)
Morphology	$> 30\%$ sperm with normal morphology
Viability	$\geq 50\%$ viable sperm
Pus cells	$< 1 \times 10^6$ /mL of semen

Who 4th edition

Parameter	Lower reference limit (range)
Semen volume (mL)	1.5 (1.4-1.7)
Total sperm number (10^6 per ejaculate)	39 (33-46)
Sperm concentration (10^6 per mL)	15 (12-16)
Total motility (PR + NP)	40 (38-42)
Progressive motility (PR, %)	32 (31-34)
Vitality (live spermatozoa, %)	58 (55-63)
Sperm morphology (normal forms, %)	4 (3.0-4.0)
Other consensus threshold values	
pH	> 7.2
Peroxidase-positive leukocytes (10^6 per mL)	< 1.0
MAR test (motile spermatozoa with bound particles, %)	< 50
Immunobead test (motile spermatozoa with bound beads, %)	< 50
Seminal zinc (μmol /ejaculate)	≥ 2.4
Seminal fructose (μmol /ejaculate)	≥ 13
Seminal neutral glucosidase (mU/ejaculate)	≥ 20

PR = progressive; NP = non-progressive; MAR = Mixed antiglobulin reaction.

2. Hormonal Evaluation when sperm is <10 million/mL

It include

- A. FSH and LH
- B. prolactin
- C. TSH
- D. estrogen
- E. Testosterone (AM) especially **bioavailable**
- F. Consider GnRH stimulation tests

- start with T + FSH } if abN, repeat with LH, estrogen, prolactin, TSH
- levels of FSH correlate with the number of spermatogonia:
 - if spermatogonia is ↓ or absent FSH are usually ↑
 - if normal, doesn't guarantee normal spermatogenesis as when spermatogonia is normal but maturation arrest exist, FSH values are within the normal range.

<u>Clinical Status</u>	<u>FSH</u> <u>(mIU/mL)</u>	<u>LH</u> <u>(mIU/mL)</u>	<u>Testosterone</u> <u>(ng/dL)</u>
<u>Normal men or obstruction</u>	<u>Normal</u>	<u>Normal</u>	<u>Normal</u>
<u>Isolated spermatogenic failure</u>	↑	<u>Normal</u>	<u>Normal</u>
<u>Testicular failure</u>	↑	↑	<u>Normal or ↓</u>
<u>Hypogonadotropic hypogonadism</u>	↓	↓	↓

ADDITIONAL TESTING

1. leukocyte staining

round cells in semen analysis **either immature germ cells (spermatocytes) or leukocytes** □ can't be differentiated without special stains

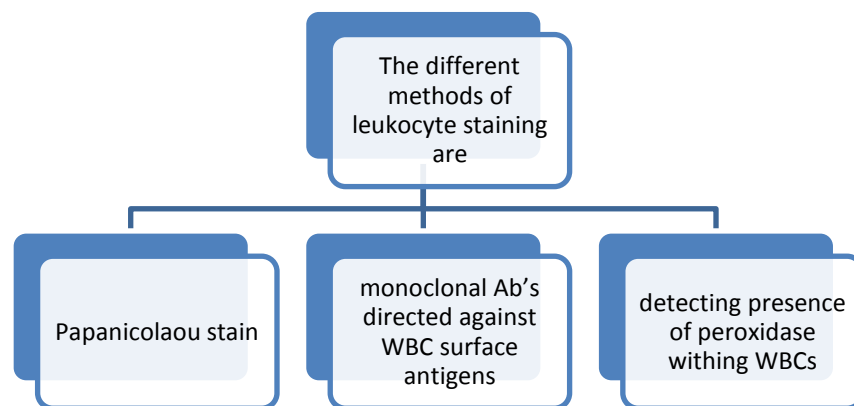
leukocyte staining is indicated if

- round cells >10-15 /HPF
 - round cells >1 million /mL
- **>1million WBCs/mL is abN *** investigate for GU tract infection is a must *****

leukocytes in semen associated with GU infection or inflammation many patients with pyospermia don't have GU

management of pyospermia in the absence of GU tract infection

- anti-inflammatories
- empirical Abx } tetracycline or doxycycline
- frequent ejaculations
- prostatic massage
- semen processing + IUI or IVF



2. Semen Cultures

Indication

- clinical symptoms suggestive of GU tract infection
- pyospermia on S/A
- isolated asthenospermia on S/A “GU tract infections is uncommon cause of male infertility but can lead to asthenospermia”

Most causative organism

- *Mycoplasma genitalium*
- *Chlamydia trachomatis*

3. Anti-sperm Ab's

indications

- 1) risk factors “tortion , truma , biopsy”
- 2) asthenospermia (shaking)
- 3) sperm agglutination
- 4) abnormal post-coital testing
- 5) couples with unexplained infertility

4. Ultrastructural Evaluation by EM

Indication

motility <5-10% associated with reasonably high viability

5. genetic testing (karyotype, CF mutation, Y microdeletions)

Indication

- unexplained infertility
- male partners of women with recurrent miscarriages
- NOA & severe oligospermia + candidate for ART TO r/o Klinefelter's, AZF microdeletions

6. Sperm Function Testing

a) Chromatin/DNA Integrity Testing

- **Idea**
 - the extent of DNA damage is measured
 - **DNA Fragmentation Index (DFI)** correlates with pregnancy rates
- **Normal and Abnormal result**
 - DFI 0%-15% □ accounted for 75% of pregnancies that occurred in 1 yr
 - DFI 15%-30% □ accounted for 22% of pregnancies that occurred in 1y
 - **DFI >30% □ accounted for only 3% of pregnancies that occurred in 1yr**

b) **post-coital sperm-cervical mucous interaction PCT**

no consensus on how test should be performed, timing, or grading

indications

- 1) hyperviscous semen
- 2) unexplained infertility
- 3) low volume semen with normal total sperm counts

the normal parameters

- 1) **>10-20 sperm/HPF**
- 2) **majority of sperm should have progressive motility**

Causes of an abnormal PCT

- inappropriate timing □ just before ovulation when cervical mucous thin and clear
- anatomic abnormalities □ hypospadias
- semen or cervical mucous anti-sperm Ab's
- inappropriate coital technique
- abnormal semen

management of abnormal PCT is IUI

c) acrosome reaction testing

- **idea**
 - it measure the capability of acrosome to penetrate oocyte
- **indications**
 - unexplained poor fertilization rates with IVF
 - unexplained infertility
 - abnormality of head morpholog
- **normal result**
 - LOW spontaneous acrosome reaction rates <5%
 - HIGH induced acrosome reaction rates of 15-40%
- Abnormal result العكس
- **management of abnormal parameter** is IVF + ICSI

d) Sperm Penetration Assays (SPA)

- **idea**
 - remove zona pellucida and count # of penetrations per hamster ova
 - tests normal sperm
 - capacitation
 - acrosome reaction
 - fusion with oolemma
 - incorporation into ooplasm
 - **doesn't test abN sperm-zona interactions**
- **indications**
 - to r/o fertilization defect when only abN'ity is morphology
 - unexplained infertility
- **management of abnormal parameter** is IVF + ICSI (no IUI or conventional IVF)

e) **other sperm function tests**

1) hemizona assay

- **idea** split zona pellucida in half and place one half with patient sperm & other half with sperm from fertile donor compare rates of bound sperm
- **result hemizona index <0.6 likely means sperm-zona interaction problem**

2) Sperm viability assay

- **idea** used to determine if sperm are dead or viable but nonmotile
- **indication**
 - sperm motility <5-10% (ultrastructural defects possible)
 - **to select viable sperm to be injected during IVF+ICSI when sperm are nonmotile**
- **result** : live sperm don't pick up dye (intact cell membrane) & swell in hypo-osmotic solution (maintain osmotic gradient)

3) Reactive Oxygen Species Testing

- elevated levels of ROS can cause sperm damage
- measure ROS vs antioxidant capacity

4) acrosomal index

- the percentage of sperm with normal acrosomes
- if < 5-15% significantly lower IVF fertilization rates
- if >5-15% >50% fertilization

Radiologic Evaluation

1. vasography

- used to identify site of obstruction in
 - azoospermic men that have Bx proven spermatogenesis
 - severely oligospermic men with suspicion of unilateral vasal obstruction with abnormal contralateral testis
- **should only be performed in conjunction with reconstructive surgery**
 - proximal patency of epididymis
 - presence of sperm in intravasal fluid Always sample this vasal fluid first to allow cryopreservation of motile sperm if found
 - distal patency
 - NS +/- dye Use indigo carmine instead of methylene blue
 - dilute contrast N if contrast seen throughout vas, SV, ejaculatory duct & bladder
 - passage of 2-0 monofilament

*****trans rectal vasography If transrectal ultrasound reveals dilated seminal vesicles and/or a midline (Mullerian duct) cyst, transrectal fine needle aspiration followed by instillation of contrast and indigo carmine should be performed. If motile sperm are found they should be cryopreserved.*****معلومه عيظه

2. TRUS

- used when suspicious of ejaculatory duct obstruction
- can visualize prostate, SVs, and ampullary portion of vas deferens
- obstruction suggested when
 - ☐ SVs are dilated abN if >1.5cm in diameter
 - ☐ **>3 motile sperm/hpf is diagnostic of ED obstruction**

3. Venography

- used to detect and treat varicoceles
- right femoral or right internal jugular access
 - R internal jugular preferred if embolization planned
 - can get false +ve if you cannulate vein or use high pressure
 - can get false -ve if not done in reverse Trendelenburg or if there's reflux from collateral veins not seen

4. scrotal U/S

- It demonstrate signs of obstruction
 - + dilatation of rete testis,
 - + enlarged epididymis with cystic lesions
 - + absent vas deferens
- it demonstrate signs of testicular dysgenesis (e.g., non- homogeneous testicular architecture and microcalcifications)
- it demonstrate associated CIS of the testis and r/o testicular tumours
- diagnose varicoceles when P/E is equivocal or it's difficult to examine pt
 - result : if >3–5mm and reversal of blood flow with Valsalva

5. abdominal U/S

- used to assess kidneys as ipsilateral renal anomalies found in 80% of men with **unilateral absence of vas** renal agenesis is most common
- not needed for patients with CBAVD + CFTR gene mutation can have renal anomalies if CBAVD that is NOT related to CF

Testicular Bx

indications

- diagnostic } ie azoospermia or severe oligospermia + N hormone profile + N-sized testes + ≥ 1 palpable vas
 - r/o obstruction
 - not recommended if suspicious of testicular failure
 - usually done bilaterally but if testicular asymmetry then done on larger testis
 - usually combined with VV or VE
- 2) diagnostic AND therapeutic } ie azoospermia + elevated FSH + bilaterally small testes
 - usually NOA
 - usually combined with sperm retrieval

*** if congenital absence of vas with normal FSH and normal-sized testes then you
SHOULD NOT do Bx because invariably normal spermatogenesis ***

normal testicular parenchyma display

- seminiferous tubules separated by thin layer of Leydig cells, blood vessels, lymphatics, and connective tissue
- Sertoli cells and spermatogonia line the BM of the seminiferous tubules

fixatives are acceptable for testicular Bx are

- 1) Bouin's
- 2) Glutaraldehyde } **formalin is NO GOOD**
- 3) Zenker's

patterns seen on testicular Bx من الاسم character

	normal testes	hypospermato genesis	maturation arrest	Sertoli cell-only syndrome	End-stage testes
seminiferous tubular	Normal Dilated in long obstruction				sclerosis
Sertoli cells	Normal	Reduced	Normal	only Sertoli cells	Present or not
germ cells	Normal	Reduced	arrest at one stage of spermatogenesis	NO germ cells	No
Leydig cells	Normal	normal	Normal	Normal	absent or decreased in #
Testis	Normal			Small to normal	atrophic firm testes
Semen analysis	Azoo	Oligo Azoo rarely	azoospermic	azoospermia	azoospermia

Other patterns are seen on testicular Bx من الاسم character

	hypogonadotropic hypogonadism	isolated LH deficiency	hypophysectomized adult males
Tubules	small		normal-sized
Leyding cell	immature Leydig cells	reduced	Absent
Germ cell	no except immature Spermatogonia	normal or hypospermatogenesis	depletion
Other			testicular atrophy

ASSISTED REPRODUCTIVE TECHNIQUES

*** involves manipulation of sperm, ova, or both

*** usually involves superovulation (controlled ovarian hyperstimulation, COH)

Sperm Retrieval

methods of retrieving sperm see surgical procedure for sperm retrieval

- ☐ advantage of frozen over fresh is **lower rate of HIV transmission**
- ☐ disadvantage of frozen over fresh is slightly lower pregnancy rates with frozen sperm

Semen Processing

methods of sperm processing prior to ART

- simple sperm washing
- swim-ups
- sedimentation
- centrifugation

types of ART

1. Intrauterine Insemination (IUI)

- injection of processed sperm into uterus
- don't use raw semen as seminal PGs may cause severe uterine cramping & may get pelvic infection
- **need AT LEAST ~2 million motile sperm after processing**

indications for IUI

- 1) male factor infertility
- 2) unexplained infertility
- 3) cervical mucous abnormalities
- 4) anatomic abnormalities interfering with deposition of sperm at cervical os
eg severe hypospadias, retrograde ejaculation
- 5) anatomic abnormalities interfering with intercourse

complications of IUI

- uterine cramping □ usually self limited
- pelvic infections □ <0.5%
- allergic reaction to insemination media □ rare
- multiple gestations if superovulation used □ 15-30%

2. IVF In-vitro fertilization

- ova harvested after ovulation via U/S-guided needle aspiration
- insemination performed in-vitro by mixing processed sperm (~100,000 sperm) with retrieved oocytes
- developing embryos incubated for 2-3 days then placed transcervically into uterus
 - recommended to transfer 2-4 embryos
- if incubated for 5 days and transferred at blastocyte stage, higher implantation rates
- **pregnancy rate only 20-30%**

3. ICSI Intracytoplasmic sperm injection

- allows for fertilization with very low numbers of sperm
- pregnancy rates 20-37%
- miscarriage rate is influence by women age ~15% in women <35yrs and 30% in >40yrs
- multiple gestations in ~40% of pregnancies

indications for IVF + ICSI

- 1) severe male factor infertility
- 2) prior failed or poor fertilization during regular IVF cycles
- 3) significant fertilizing ability defects (eg sperm-zona interaction issues)

side effects of IVF + ICSI

- low birth weight singletons
- MSK defects
- CV defects
- hypospadias
- multiple gestations in ≥30%

Idiopathic Infertility

patients of male infertility will still have no discernible cause for abnormal semen analyses

incidence more than 30%

Empiric Medical Therapy it include shown to be ineffective ☐ if started, continue for 3-6 months

- Gonadotropin-releasing hormone
- Gonadotropins
 - Luteinizing hormone (human chorionic gonadotropin)
 - Follicle-stimulating hormone (human menopausal gonadotropin)
- Antiestrogens
 - Clomiphene citrate
 - Tamoxifen citrate
- Aromatase inhibitors especially in patient testosterone to estradiol < 10 and obese patient
 - Testolactone
 - Anastrozole
- Other
 - Antioxidant vitamins
 - L-carnitine
 - Kallikrein
 - Thyroid hormone
 - Dopamine agonist for hyperprolactin-associated infertility
 - Bromocriptine
 - Cabergoline

Y-chromosome and male infertility

- three regions termed AZFa, AZFb and AZFc detected on the long arm of the Y chromosome In each AFZ region, there are several spermatogenesis genes.
- AZFc deletions are most common (approximately 65-70%), followed by deletions of the AZFb and AZFb+c or AZFa+b+c regions (25-30%). AZFa region deletions are extremely rare (5%).

Clinical implications of Y microdeletions

- Complete removal of the AZFa region is associated with severe testicular phenotype (Sertoli cell only syndrome),
- complete removal of the AZFb region is associated with spermatogenic arrest.
- Complete removal of the AZFc region causes a variable phenotype ranging from azoospermia to oligozoospermia.

If complete AZFa or AZFb microdeletions are detected, micro-TESE is not necessary because sperm will not be found. AZFc (distal) best prognosis for sperm retrieval (hypospermat.)

Indications for AZF deletion screening are

- azoospermia
- severe oligozoospermia (spermatozoa count < 5 million/mL).

Genetic counselling for AZF deletions

- genetic counseling in the male offspring is mandatory. As any Y-deletions are transmitted obligatorily to male
- There is risk for any offspring to develop 45,X0 Turner's syndrome and ambiguous genitalia.
- fup of male children is needed with cryopreservation of spermatozoa at a young age .

Y-chromosome: 'gr/gr' deletion

- deletion removes half of the gene content of the AZFc region, known as the gr/gr deletion
- There was eightfold higher risk of developing oligozoospermia also testicular germ cell tumours

Treatment IVF/ICSI

Cystic fibrosis mutations and male infertility

Cystic fibrosis (CF) is a fatal autosomal-recessive disorder.

CF transmembrane conductance regulator (CFTR) gene located on chromosome 7p.

This gene function is the formation of the ejaculatory duct, seminal vesicle, vas deferens and distal two-thirds of the epididymis.

Congenital bilateral absence of the vas deferens (CBAVD) is associated with CFTR gene mutations in 90%

When a man has CBAVD, it is important to test him and his partner for CF mutations as

	carrier of CFTR mutations	having a child with CF or CBAVD	
female partner	+ve	50%	carefully when ICSI using the husband's sperm,.
Female paertener	-ve	0.4%	

Unilateral or bilateral absence/abnormality of the vas and renal anomalies.

- In unilateral and bilateral absence of vas deferens an abdominal ultrasound should be undertaken. Findings may range from ipsilateral absence of the kidney, to bilateral vessel abnormalities and renal abnormalities, such as pelvic kidney .

absence of the vas deferens	kidney	CFTR mutation screening
Unilateral	Ipsilateral absence “usually associated ”	not indicated
unilateral	normal kidneys	indicated

OBSTRUCTIVE AZOOSPERMIA

Definition: It is the absence of spermatozoa and spermatogenic cells in semen and post-ejaculate urine due to bilateral obstruction of the seminal ducts.

Incidence

- 15-20% of men with azoospermia
- OA is less common than NOA .

Classification and etiology

Causes of obstruction	Incidence	Congenital	acquired
Intratesticular	15-25%	(dysjunction between rete testis and efferent ductules)	post-inflammatory post-surgical
Epididymal	30-70%	- CBAVD usually associated with epididymal and SV agenesis - disjunction between efferent ductules and the corpus epididymis - agenesis/atresia of a short part of the epididymis. - (Young's syndrome) chronic sinopulmonary infections in which obstruction results from a mechanical blockage due to debris within the proximal epididymal lumen.	Post inflammatory (e.g., gonococcal or chlamydial) Post surgical e.g cyst removal.
Vas deferens		CBAVD	post surgical as hernia repair or vasectomy
Ejaculatory duct	1-3%	atresia, stenosis, utricular/ mullerian /wolffian duct cyst	post inflammation, post surgical (eg TURP)
Functional obstruction of the distal seminal ducts		• It is due to local neuropath. So usually associated with urodynamic dysfunction • It is usually presented in juvenile diabetes and polycystic kidney diseases	

Congenital Cystic obstructions

Mullerian duct cyst	Wolffian duct cyst
medially located in the prostate between the ejaculatory ducts	Paramedian or lateral intraprostatic cysts
the ejaculatory ducts are laterally displaced and compressed by the cyst	rare in clinical practice

In 25% of men with a suspected obstruction, no spermatozoa are found in the epididymis during scrotal exploration, indicating an intratesticular obstruction or non-obstructive

Diagnosis

History As usual +Patients should be asked about:

- ✚ Haematospermia
- ✚ Post ejaculatory pain
- ✚ Obstructive or irritative LUT
- ✚ Urethritis or prostatitis
- ✚ Previous scrotal or hernia surgery
- ✚ Chronic sinopulmonary infection

examination

- at least one testis with a volume > 15 ml, although a smaller testicular volume may be found in some patients with OA and concomitant partial testicular failure;
- epididymis enlarged , hard and nodular
- vas
 - nodules
 - absence or partial atresia of the vas;
- prostatic abnormalities.
- Urethra signs of urethritis;

Investigation

1- Semen analysis,

- vary between azoospermia, and severe OAT syndrome.
- S/A findings that suggest obstruction
 - low volume azoospermia
 - acidic pH acidic prostatic secretions (SV secretions are alkaline)
 - no or low fructose (<120mg/dL) fructose
 - semen doesn't coagulate (from lack of SV fluid)

2- Hormone levels

- Serum FSH levels may be normal,

3- Scrotal Ultrasonography

4- TRUS

TRUS should be performed at high resolution and with high-frequency (> 7 MHz) biplane transducers.

- **SVs >1.5cm means obstruction**
- **SV aspiration with >3 motile sperm/hpf is diagnostic of ED obstruction**

5- Testicular biopsy

- It is indicated to exclude spermatogenic failure.
- Testicular biopsy should be combined with extraction of testicular spermatozoa .
- A scoring system for testicular biopsies is provided (e.g., Johnsen Score) .

Score	Histological criteria
10	Full spermatogenesis
9	Slightly impaired spermatogenesis, many late spermatids, disorganised epithelium
8	< 5 spermatozoa per tubule, few late spermatids
7	No spermatozoa, no late spermatids, many early spermatids
6	No spermatozoa, no late spermatids, few early spermatids
5	No spermatozoa or spermatids, many spermatocytes
4	No spermatozoa or spermatids, few spermatocytes
3	Spermatogonia only
2	No germinal cells, Sertoli cells only
1	No seminiferous epithelium

Treatment according to level of obstructin

Intratesticular obstruction

- TESE allows sperm retrieval is recommended. The spermatozoa retrieved may be used immediately for ICSI or be cryopreserved.

Epididymal obstruction

- end-to-end or end-to-side microsurgical intussusception epididymovasostomy is recommended,. Anatomical recanalisation require 3-18 months following surgery.
- TESE and PESA in case of surgical failure.

Proximal vas obstruction

- Usually post vasectomy microsurgical Vasovasostomy.
- The absence of spermatozoa in the intraoperative vas deferens fluid suggests the presence of a secondary epididymal obstruction; especially if the seminal fluid of the proximal vas has a thick “toothpaste” appearance

Distal vas deferens obstruction

- It is usually post hernia repair and usually large defect, surgery is impossible so
- proximal vas deferens sperm aspiration or TESE/MESA.
- crossover vasovasostomy or tubulovasostomy In large unilateral vas deferens defects associated with contralateral testicular atrophy can be used
- Microsurgical epididymal sperm aspiration (MESA) is indicated in men with CBAVD.

Ejaculatory duct obstruction

The treatment depends on its aetiology.

- 1- Transurethral resection of the ejaculatory ducts is indicated in
 - large post-inflammatory obstruction
 - one or both ejaculatory ducts empty into an intraprostatic midline cyst.
- 2- obstruction due to a midline intraprostatic cyst, incision or unroofing of the cyst.
- 3- functional obstruction of the distal seminal ducts, Spermatozoa can then be retrieved by antegrade seminal tract washout as TURED often fails to improve sperm output.

Complications following TURED include

- retrograde ejaculation due to bladder neck injury
- urine reflux into the ejaculatory ducts, seminal vesicles, and vasa (causing poor sperm motility, semen acid pH, and epididymitis).

The alternatives to TURED are

- MESA, TESE,
- proximal vas deferens sperm aspiration,
- seminal vesicle ultrasonically guided aspiration,
- direct cyst aspiration.

We can perform TURED in 2 ways

- 1) under TRUS guidance
- 2) inject indigo carmine into SVs, remove TRUS and resect until blue dye seen in urethra

VARICOCELE

- 15% of normal male population
- 25% of men with abnormal semen parameters
- 40% of infertile men
- 70% of patients with 2° infertility
- 90% left sided, 10% bilateral

It is more common on the left due to

- 1) left gonadal vein enters left renal at right angle
- 2) absence of venous valves more common on left side
- 3) left renal vein more susceptible to compression between SMA and aorta
 - “nutcracker phenomenon”

andrological implications of varicocele:

- failure of ipsilateral testicular growth and development;
- symptoms of pain and discomfort;
- infertility
 - + decreased motility
 - + decreased sperm number up to azospermia
 - + increased abN morphology (tapered forms)
 - + increased sperm DNA damage, as varicocele-mediated oxidative stress.
 - + Leydig cell dysfunction
 - + histologic changes } tubular thickening, interstitial fibrosis, MA, etc

theories on how varicoceles impair fertility

- 1) ↑'d intratesticular temperature
- 2) reflux of renal & adrenal metabolites
- 3) ↓'d blood flow & hypoxia
- 4) paracrine hormonal insufficiency
- 5) impaired growth

Classification

- subclinical: not palpable or visible at rest or during valsalva manoeuvre, but can be shown by special tests (Doppler ultrasound studies) ; no study shows improved pregnancy
- grade 1: palpable during valsalva manoeuvre, but not otherwise;
- grade 2: palpable at rest, but not visible;
- grade 3: visible and palpable at rest.

Diagnosis

The diagnosis of varicocele is made by clinical examination and should be confirmed by colour Doppler analysis

varicoceles due to venous occlusion (eg RCC + IVC thrombus) DO NOT collapse when in supine position

Varicocelectomy

varicocele treatment in infertile men who have normal semen analysis or in men with subclinical varicocele. In this situation, varicocele treatment cannot be recommended.

However, The duration of infertility in this group seems to be important. couples with infertility of > 2 years duration had a significantly higher pregnancy rate after surgery compared to couples with an uncorrected varicocele. In couples with a shorter duration of infertility, such a difference was not observed.

Varicocele repair may be indicated in

- men with subnormal semen analysis,
- a clinical varicocele ,
- infertility duration of > 2 years
- otherwise unexplained infertility.

Varicocele repair in adolescent

- there is a significant risk of overtreatment: most adolescents with a varicocele will have no problem achieving pregnancy later in life.
- Varicocele treatment is recommended for adolescents with progressive failure of testicular development documented by serial clinical examination

Treatment

varicocelectomy

- get improved semen parameters (70%)
 - the larger the varicocele, the more likely improvement in semen quality
 - **first improved counts, then motility;** less commonly morphology improvement
- ↑'d testicular volume
- can also improve testosterone levels and decrease FSH
- conception rates average ~40-50% (vs baseline 30%)
- ~10% of azoospermic patients get enough sperm after Sx for IUI

important points to consider when assessing a child with a varicocele

- testicular volume
 - main criteria used for management decisions
 - semen analysis and hormone stimulation testing not practical in kids
 - N size differential can be up to ~20% of volume or 2mL
- testicular consistency
- contralateral side

indications to treat a pediatric varicocele

- ipsilateral testis >20% or >2mL smaller than contralateral testis
- painful varicocele

Treatment	Ref.	Recurrence/ persistence %	Complication rates
Antegrade sclerotherapy	18	9	Complication rate 0.3-2.2%: testicular atrophy, scrotal haematoma, epididymitis, left-flank erythema
Retrograde sclerotherapy	19	9.8	Adverse reaction to contrast medium, flank pain, persistent thrombophlebitis, vascular perforation
Retrograde embolisation	20,21	3.8-10	Pain due to thrombophlebitis, bleeding haematoma, infection, venous perforation, hydrocele, radiological complication (e.g. reaction to contrast media), misplacement or migration of coils, retroperitoneal haemorrhage, fibrosis, ureteric obstruction
<i>Open operation</i>			
Scrotal operation		-	Testicular atrophy, arterial damage with risk of devascularisation and gangrene of testicle, scrotal haematoma, post-operative hydrocele
Inguinal approach	22	13.3	Possibility of missing out a branch of testicular vein
High ligation	23	29	5-10% incidence of hydrocele (< 1%)
Microsurgical inguinal or subinguinal	24,25	0.8-4	Post-operative hydrocele arterial injury, scrotal haematoma
Laparoscopy	26,27	3-7	Injury to testicular artery and lymph vessels, intestinal, vascular and nerve damage, pulmonary embolism, peritonitis, bleeding, post-operative pain in right shoulder (due to diaphragmatic stretching during pneumoperitoneum), pneumoscrotum, wound infection

DISORDERS OF EJACULATION

Classification and aetiology

1) Anejaculation

- It involves complete absence of antegrade or retrograde ejaculation due to failure of semen emission from the seminal vesicles, prostate and ejaculatory ducts into the urethra.
- It is usually associated with a normal orgasmic sensation. Occasionally this sensation is altered or decreased (e.g., in incomplete spinal cord injuries).
- Causes .

Neurogenic	Drug-related
Spinal cord injury	Antihypertensives
Cauda equina lesion	Antipsychotics
Retroperitoneal lymphadenectomy	Antidepressants
Aortoiliac or horseshoe-kidney surgery	Alcohol
Colorectal surgery	
Multiple sclerosis	
Parkinson's disease	
Autonomic neuropathy (diabetes mellitus)	

2) Delayed ejaculation

- abnormal stimulation of the erect penis is needed to achieve orgasm with ejaculation
- it can be considered a mild form of anorgasmia, and both conditions can be found alternately in the same patient.
- causes
 - ✚ psychological,
 - ✚ organic (e.g., incomplete spinal cord lesion)
 - ✚ iatrogenic penile nerve damage
 - ✚ pharmacological [e.g., selective serotonin re-uptake inhibitors (SSRIs), antihypertensives, or antipsychotics.

3) Anorgasmia

- It is the inability to reach orgasm and can give rise to anejaculation.
- Anorgasmia is often a primary and its cause is usually psychological

4) Retrograde ejaculation

- It is the total, or sometimes partial, absence of antegrade ejaculation as a result of semen passing backwards through the bladder neck into the bladder.
- Patients experience a normal or decreased orgasmic sensation, except in paraplegia.
- Causes

Neurogenic	Pharmacological
Spinal cord injury	Antihypertensives
Cauda equina lesions	α 1-adrenoceptor antagonists
Multiple sclerosis	Antipsychotics
Autonomic neuropathy (juvenile diabetes)	Antidepressants
Retroperitoneal lymphadenectomy	Bladder neck incompetence
Sympathectomy	Congenital defects/dysfunction of hemitrigone
Colorectal and anal surgery	Bladder extrophy
Urethral	Bladder neck resection
Ectopic ureterocele	Prostatectomy
Urethral stricture	
Urethral valves or verumontanum hyperplasia	
Congenital dopamine β -hydroxylase deficiency	

5) Asthenic ejaculation

It is partial ejaculatory incompetence or “ejaculation baveuse” and is characterised by an altered propulsive phase, with a normal emission phase.

The orgasmic sensation is reduced and the typically rhythmical contractions associated with ejaculation are missing,

Asthenic ejaculation does not affect semen quality.

Causes as causes of retrograde ejaculation

6) Premature ejaculation(PE).

7) Painful ejaculation

- It is usually an acquired condition that is often related to lower urinary tract symptoms.
- The painful sensation might be felt in the perineum, or urethra and urethral meatus
- Causes
 - ✚ ejaculatory duct obstruction,
 - ✚ all types of chronic prostatitis/CPPS,
 - ✚ urethritis,
 - ✚ urethrocele,
 - ✚ antidepressant drugs
 - ✚ psychological problems.

Diagnosis

A. Clinical history

The patient must be carefully checked for diabetes, neuropathy, trauma, urogenital infection, previous surgery, and medication.

micturition and ejaculation (presence of nocturnal emission, ejaculatory ability in given circumstances, and primary or acquired disorder),

psychosexual aspects (education, features of affective relationship, pre-existent psychological trauma, and previous psychological therapy).

B. Physical examination

Genital and rectal examinations are conducted, evaluation of the prostate, bulbocavernosus reflex, and anal sphincter tone.

Minimal neurological tests include:

- sensitivity of scrotum, testes, and perineum
- cremasteric and abdominal cutaneous reflex
- leg osteotendinous and plantar reflexes.

C. Investigation

1- Post-ejaculatory urinalysis

Post-ejaculatory urinalysis of centrifuged urine can be used to determine if there is total or partial retrograde ejaculation.

2- Microbiological examination

Initial, mid-stream urine, EPS, and/or urine after prostatic massage are cultured for evidence of prostatic infection.

3- Optional diagnostic work-up

It include

- neurophysiological tests (bulbocavernosus evoked response and dorsal nerve somatosensory evoked potentials);
- tests for autonomic neuropathy;
- psychosexual evaluation;
- video-cystometry;
- cystoscopy;
- transrectal ultrasonography;
- uroflowmetry;
- vibratory stimulation of the penis.

Treatment

1- Premature ejaculation see later

2- Retrograde ejaculation

- the patient can be encouraged to ejaculate when his bladder is full to increase bladder neck closure
- In the absence of spinal cord injury, anatomical anomalies of the urethra, or pharmacological agents, drug treatment must be used to induce antegrade ejaculation

Drug	Dosage regimen
Ephedrine sulphate	10-15 mg four times daily
Midodrin	5 mg three times daily
Brompheniramine maleate	8 mg twice daily
Imipramine	25-75 mg three times daily
Desipramine	50 mg every second day

- Sperm collection from post-orgasmic urine for use in ART is recommended if:
 - ✚ drug treatment is ineffective or intolerable as a result of side effects;
 - ✚ the patient has a spinal cord injury;
 - ✚ drug therapy inducing retrograde ejaculation cannot be interrupted.;

Sperm retrieval is timed to coincide with the partner's ovulation. Urine must be alkalinised (pH 7.2-7.8) and osmolarity must be 200-300 mOsmol/kg. Alternatively, a catheter can be inserted into the bladder to allow instillation of 10-50 mL Tyrode's or Ham's F-10 medium. The patient must ejaculate, and a second catheterisation is carried out immediately to retrieve spermatozoa.

- If the biological sperm preparation is not of sufficient quality for IUI , in vitro reproductive procedures (e.g., ICSI) with fresh or cryopreserved spermatozoa.

3- Anejaculation

Drug treatment usually not effective.

vibrostimulation (i.e., application of a vibrator to the penis) is first-line therapy.

- It evokes the ejaculation reflex, which requires an intact lumbosacral spinal cord segment. So Complete spinal injuries and injuries above T10 show a better response

electroejaculation If vibrostimulation has failed, is the therapy of choice.

- It involves electrical stimulation of the periprostatic nerves via a probe inserted into the rectum, which seems unaffected by reflex arc integrity.
- Anaesthesia is required except in cases of complete spinal cord injury.
- In 90% of patients, electrostimulation induces ejaculation, which is retrograde in one-third of cases.

If the quality of semen is poor, or ejaculation is retrograde, the couple may enter an IVF programme.

SEMEN CRYOPRESERVATION

It is the storage of biological material at subzero temperatures [e.g., -80 or -196°C (the boiling point of liquid nitrogen)], at which biochemical processes of cell metabolism are slowed or interrupted.

Indications for storage

- 1- Before potentially sterilising chemotherapy or radiotherapy for cancer or for non-malignant
- 2- diseases.
- 3- Before surgery that might interfere with fertility (e.g. bladder neck surgery in a younger man or removal of a testical in a man with testicular malignancy, before vasectomy).
- 4- For men with progressive decrease in semen quality as a result of diseases that have an associated risk of subsequent azoospermia (i.e. pituitary macroadenoma, Craniopharyngioma, empty sella syndrome, chronic nephropathy, uncontrolled diabetes mellitus, multiple sclerosis).
- 5- For men with paraplegia when sperm have been obtained by electro-ejaculation or obtained by using penile vibratory stimulation.
- 6- For men with psychogenic anejaculation, after sperm have been obtained either by electro-ejaculation or a sperm retrieval procedure.
- 7- After gonadotrophin treatment has induced spermatogenesis in men with hypogonadotropic hypogonadism.
- 8- For men with NOA, thus avoiding unnecessary hyperstimulation of the female partner. It can also be used to avoid repeated sperm retrieval procedures.
- 9- In any situation where sperm have been obtained by a sperm retrieval procedure (e.g. after failed vasectomy reversal, or in some cases of epididymal obstruction not amenable to surgery).
- 10- For storage of donor sperm, because cryopreservation and a quarantine period of 3-6 months reduces the risk of transmission of infection from sperm donors; in most countries, fresh sperm are no longer used

Precautions and techniques

Freezing and thawing process

The cryopreservation techniques currently used are not yet optimal because damage occurs to cells during cryopreservation and prolonged storage.

Major causes of damage during freezing are

- ice crystal formation and cell dehydration, which disrupt the cell wall and intracellular organelles.
- damage done to sperm DNA
- contamination of samples with microorganisms and high levels of superoxide radicals

To reduce ice crystal formation,

- a cryopreservation solution contain varying proportions of glycerol and albumin is added before freezing.
- After freezing, the samples are immersed in liquid nitrogen.

To reduce damage caused by freezing and thawing, including:

- Rapid method: sample is held in the vapour phase for 10 minutes before being plunged into liquid nitrogen.
- Slow method: sample is gradually cooled in the vapour phase for approximately 40 minutes.
- Programmable automatic freezing machine, which is preset to cool at a rate of 1-10°C/min, is used.

Testing for infections and preventing cross-contamination

samples should be tested for hepatitis B and C and human immunodeficiency virus (HIV). In case of non-partner donation, samples are also tested for C. Trachomatis and syphilis, cytomegalovirus .

Fail-safe precautions to prevent loss of stored materials

This is important for sperm stored before potentially sterilising cancer chemotherapy because these patients may not be able to obtain further sperm.

Further improvement can be achieved by selecting sperm with the best motility and DNA integrity and freezing these sperm in seminal plasma

Cryopreservation of testicular stem cells

Spermatogonial stem cell (SSC) preservation and transplantation have been proposed as a promising strategy for fertility preservation in young boys facing SSC loss .

Cryopreservation protocols for testicular tissue is under investigation

stem cell transplantation methods are being used in human testes, under investigation

Recommendations

Cryopreservation of semen should be offered to all men who are candidates for chemotherapy, radiation or surgical interventions that might interfere with spermatogenesis or cause ejaculatory disorders.

If testicular biopsies are indicated, sperm cryopreservation is strongly advised.

If cryopreservation is not available locally, patients should be advised about the possibility of visiting, or transferring to, the nearest cryopreservation unit before therapy starts.

Consent for cryopreservation should include a record of the man's wishes for his samples if he dies or is otherwise untraceable.

Precautions should be taken to prevent transmission of viral, sexually transmitted or any other infection by cryostored materials from donor to recipient, and to prevent contamination of stored samples. These precautions include testing of the patient and the use of rapid testing and quarantine of samples until test results are known. Samples from men who are positive for hepatitis virus or HIV should not be stored in the same container as samples from men who have been tested and are free from infection.

MALE CONTRACEPTION

Methods and first-year failure rate of male contraception

- withdrawal 19%,
- periodic abstinence 20%,
- condoms 3-14%)

hormonal male contraception “under investigation”

it is based on the suppression of gonadotropins and testosterone substitution to maintain male sexual function and bone mineralization, and to prevent muscle wasting

Various methods

- testosterone monotherapy,
- androgen/ progestin combinations,
- testosterone with GnRH analogues,
- selective androgen- and progestin-receptor modulators.

There are racial differences in the response to androgens alone. However, a combination of testosterone with progestin results in complete suppression of spermatogenesis in all races,

Vasectomy “gold standard for the male contraception.” Surgical techniques see surgical procedure

some diseases involving the URT that are associated with male infertility

1) Kartagener's syndrome

- ☐ form of primary ciliary dyskinesia } aka "immotile cilia syndrome"
- ☐ **immotile sperm (inner dynein arm problem)** + frequent URTIs + situs inversus

2) CF

- ☐ congenital bilateral absence of vas (**CBAVD**)
- ☐ motile sperm

3) Young's syndrome

- ☐ **azoospermia (secretions block epididymis)** + frequent URTIs
- ☐ motile sperm

4) Sarcoidosis

- ☐ pulmonary disease
- ☐ azoospermia (obstructive)